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SHOULD THE UNITED STATES PHARMACOPŒIA RECOGNIZE VERATRUM ALBUM AND VERATRUM VIRIDE AS ONE DRUG?

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AND

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THE question has been raised, in the committee upon the revision of the Pharmacopœia, whether it would be proper for the *United States Pharmacopœia* to allow of the substitution of veratrum album for veratrum viride. The botanical characteristics of the two plants are so similar as to make it probable that they really represent one species. The differences in the histological character of the root, as reported upon by Dr. R. H. Denniston to the Committe on Revision, do not seem to us sufficient to indicate distinctness, and indeed may very probably depend upon accidental influences during growth, such as differences of soil, of moisture, and of age. Specific identity, of course, does not prove exact similarity of physiological powers in two plants, as it is well known that a plant may fail in the production of its active principles under unfavorable circumstances. The hemp of the South and the hemp of the North are medically essentially different in that one is powerful and the other weak. We know of no case, however, in which it has been demonstrated that the same plant is, under different circumstances, possessed of different physiological powers; or, in other words, is capable of producing diverse physiologically active principles.

In the case of the Veratrums of Europe and America it is easily to be conceived that the irregularities in the development of the active principles may result in the production of different physiological activities, because each of these plants has two active alkaloids in them, differing in their physiological range, so that if plant A should produce very largely of the alkaloid X and fail to develop the alkaloid Y, its relations with the human system would be very different from plant B, which produces largely of the alkaloid Y and but little of the alkaloid X.

Under the circumstances, therefore, it is entirely possible that Veratrum album and Veratrum viride may be specifically identical and physiologically diverse, so that only by chemical, clinical, and physiological experiments can their relative values in the sick-room be determined. Denniston states that Veratrum album contains about five times as much alkaloid as does Veratrum viride; but, as we shall show later, it is probable that the alkaloidal strength of each drug varies very greatly in union with differences of climate and soil, and especially in proportion as the individual specimen is composed solely of rhizomes or contains masses of comparatively inert rootlets. Prof. Kraemer is, we believe, about to undertake a chemical study of the present subject, so that we shall know more from the chemical stand-point.

The symptoms which are produced by poisonous doses of Veratrum viride are certainly in many respects similar to those which have been noted as present in the recorded cases of poisoning with the Veratrum album or white hellebore. It is commonly stated, however, that in poisoning with Veratrum viride the bowels are not disturbed, while there is uniformily violent purgation after the toxic dose of Veratrum album. This difference, however, appears not to be as constant as has been believed. Thus, while it seems certain that there is usually little or no effect produced by the largest doses of Veratrum viride upon the intestinal tract, the cases reported by Dr. E. M. Pendleton and by Dr. E. Platt (*Stillé's Therapeutics*, vol. ii., fourth edition, p. 296) show that occasionally Veratrum viride does produce very watery evacuations. On the other hand, an examination of recorded cases shows that white hellebore or Veratrum album does not always purge, as shown in the case reported by Dr. Rayner, also cited by Prof. Stillé. Further, in six cases of poisoning reported by Mavel (*Journ. de Chim. Méd.*, 1851, third series, vii. p. 586); in one reported by M. A. Chevallier (*Ann. d'Hyg.* Paris, 1877, second series, xlviii. p. 459), and in one reported by J. Giles (*Lancet*, Lond., 1857, ii. p. 9), purging appears not to have been present. On the other hand, in three cases which were medicolegally examined and reported upon by Nivet and Giraud (*Gaz. Hebd. de Méd.* Paris, 1861, viii. p. 499), there was much purging, in one instance with excessive tenesmus and bloody stools. In a case reported by Dr. E. Peugnet (*New York Medical Record*, 1872, vol. ii.), in which half an ounce of the homœopathic mother tincture of Veratrum album was taken, the purging was excessive, and both vomit and stools contained blood.

The truth would seem to be that purging may be produced by the toxic dose of either Veratrum viride or Veratrum album; but whereas it is a rare symptom in Veratrum viride poisoning, it is a common symptom in poisoning by Veratrum album; further, in so far as we know, in no case of Veratrum viride poisoning has the purging been so severe as it frequently is in poisoning by Veratrum album.

For the purposes of experimental research we were furnished by Prof. Henry Kraemer with three specimens, 500 grammes each, of No. 1, veratrum viride; No. 2, Veratrum album, with the rhizome only; No. 3, veratrum album, with the rhizome and roots. From these crude drugs were made, under the supervision of Prof. Remington at the College of Pharmacy, fluid extracts which were used by us. The first series of experiments was made upon frogs. The results were entirely concordant, and it is, of course, not necessary here to give in detail more than two experiments as examples The frogs used were of the same species; were taken without selection out of a large lot originally obtained for the purposes of the physiological laboratory of the University of Pennsylvania, some weeks before the date of our experiments, and kept in a well-regulated frog-cage.

In the first series uninjured frogs were employed; in the second Turck's method was used.

EXPERIMENTS OF DECEMBER 29.

	Veratrum Album (Phila.).		*Veratrum Viride.*
Time	Frog weighed 26.5 gm.	Time.	Frog weighed 39.5 gm.
3.34	Injected 0.50 c.c. into posterior lymph sac (some escaped).	3.35	Injected 0.75 c.c. (some lost).
3.35	Paralysis of right hind leg.		
3.37	Paralysis of both hind legs; do not respond to strong HNO_3	3.38	Reflexes much diminished, but not gone.
		3.28½	Reflexes gone in hind legs, do not respond to strong HNO_3.
3.38	Reflexes gone in front legs.	3.39	Reflexes gone in front legs; eye reflexes present.
		3.40	Convulsive movements.
3.42	Eye reflexes gone, heart still beating.	3.41	Eye reflexes gone, heart still beating.

TURCK'S METHOD.

Metronome beats 160 per minute, ¼ per cent. H_2SO_4 to test reflexes.

Veratrum Album.

Frog weighed 28.0 gm.

Time.	Reaction time.
3.50	6 beats.
3.56	6 beats.
4.01	7 beats.
4.04	7 beats.
4.06	Injected ¼ c.c. of 50 per cent. solution of v. album.
4.08	7 beats.
4.13	21 beats, response feeble, right foot.
4.16	13 beats for left foot.
4.17	40 beats (right foot), no response.
4.20	23 beats (left foot), feeble response. ½ per ct. acid used, both feet immersed.
4.23	10 beats.
4.26	13 beats.
4.29	15 beats, feeble response.
4.32	No response.
4.35	No response to 50 per cent. H_2SO_4; strong convulsions when probe run down spine.

Veratrum Viride.

Frog weighed 27.0 gm.

Time.	Reaction time.
3.53	5 beats.
3.57	7 beats.
4.02	6 beats.
4.05	5 beats.
4.07	Injected ¼ c.c. of 50 per cent. solution of v. viride.
4.10	5 beats.
4.14	9 beats.
4.18	10 beats, right foot,
4 19	40 beats (left foot), no response.
4.21	40 beats (right foot), no response.
4.24	No response.
4.25	No response to 50 per cent. H_2SO_4.

Slight convulsion when probe run down spine.

So far as our experiments upon frogs are concerned, no qualitative differences could be perceived between the action of the two veratrums. An inspection of the experiments given above will show that if there be any inequality of strength the Veratrum viride is the more powerful. Qualitative experiments, however, upon the lower animals are apt to be misleading, because of the differences in the rate of absorption and of susceptibility in different individuals of the same species; and, in order to reach any conclusion from frogs, much more numerous experiments would have to be made than it seemed to us worth while to do. Further, the results obtained in experiments not here detailed did not agree with those above given, the Veratrum album appearing in some cases to be stronger than veratrum viride. On the whole, our experiments lead to the conclusion that there is no distinct qualitative or quantitative difference in the action of Veratrum album and Veratrum viride upon frogs.

In the next series of experiments mammals were poisoned without the performance of any operative procedures.

The general experiments upon the lower animals were made with Veratrum album (eight) and with Veratrum viride (three) upon rabbits, and one experiment with Veratrum album upon a dog. A greater number of experiments were made with Veratrum album, on account of our familiarity with the effects from previous experiments with Veratrum viride. The symptoms did not differ in the two cases. After small, fatal doses there was a progressive weakness, lessened reflexes, accompanied in the rabbit with peculiar movements, resembling those of vomiting, and in the dog by vomiting. After very large fatal doses there were violent convulsions, with paralysis, and death by failure of the respiration, although the heart was, throughout the poisoning, profoundly affected.

In no case was there violent purging produced either by Veratrum viride or Veratrum album. In some of the cases of Veratrum viride poisoning there was a slight discharge of normal feces, while very moderate purging was occasionally noted in poisoning with Veratrum album.

As already stated, comparative experiments to settle the relative strength of a drug, unless carried out on a very large scale, are of very little value. The results of the experiments are, however, shown in the following table, which would appear to demonstrate that the Veratrum album bought in New York is very much stronger than the Veratrum album bought in Philadelphia, this latter being about the same strength as Veratrum viride. The Veratrum album bought in New York was composed simply of rhizomes; the Veratrum album bought in Philadelphia contained very many rootlets. As the alkaloids are chiefly found in the rhizomes, it is evident that the strength of a fluid extract must largely depend upon whether the crude drug from which it has been produced is composed solely of rhizomes or largely of rootlets.

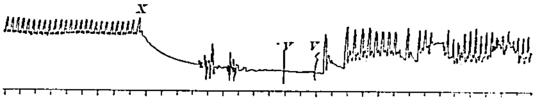
Dose per kilo.	Veratrum album (Philadelphia).	Veratrum album (New York).	Veratrum viride.
0.20 c.c.	....	Death in 20 minutes.	
0.25 "	Death in 42 minutes.	Death in 14 minutes.	
0.5 "	Death in 25 minutes.		
0.75 "	....	....	Death in 16 minutes.
1.0 "	Death in 14 minutes.	....	Death in 12 minutes.

The next series of experiments were manometrical studies in regard to the effect of drugs upon blood-pressure. Of these we have made a large number, but have not been able to perceive any distinct difference in the action of Veratrum album and Veratrum viride upon the circulation. The general effects are for the most part concordant with the results of previous investigators, the only point in which the effects differed from what we expected being in the first action of a very large dose upon the inhibitory cardiac nerves.

It is now many years since Dr. H. C. Wood published his articles upon the action of the alkaloids of Veratrum viride. In these it was noted that the veratroidine was an extremely powerful stimulant to the inhibitory nerves, so that it was possible to produce by it a cardiac arrest, which was immediately put an end to by section of the vagi. It has been generally believed, however, that the veratroidine was in such small proportion in the drug that its action could not be demonstrated with cruder preparations than the separated alkaloid. We append, however, two tracings (Figs. 1 and 2), made with a Hürthl spring manometer, Veratrum album having been used in the one, Veratrum viride in the other. The similarity of the action will be at once apparent, only the results following the section of the vagi seem to be a little more pronounced in the case in which Veratrum album was used. The doses in the two experiments were very nearly the same—kilo for kilo.

From our manometrical studies we would state the following conclusions: First, Veratrum viride and Veratrum album act similarly upon the circulation; second, after each the respirations usually cease before the heart-beats, though occasionally the reverse happens, and when artificial respiration is practised there is finally diastolic cardiac arrest; third, any dose of either poison which is sufficient to produce a demonstrable effect upon the circulation causes a fall of arterial pressure which, at least in its early stages, is not solely or chiefly due to the vasomotor paralysis, since asphyxia produces an immediate rise of mercury in the manometer. Later in the poisoning, if the dose has been large enough, vasomotor paralysis is developed, since asphyxia, even while the heart is still acting with some force, is powerless to elevate the arterial pressure. When the poison is injected directly into the jugular vein there is an immediate fall of the arterial pressure, the extent of the fall depending upon the dose. The heart may be arrested at once, and, when exposed, be incapable of responding at all to stimuli; or there may be a cardiac arrest, which finally recovers itself completely, or which at once disappears upon section of the vagi.

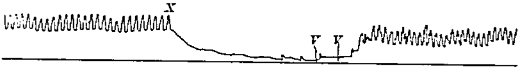
FIG. 1.



Hürthl spring manometer.

Dog, weight 10.3 kilos. X injection of 1.5 c.c. of 25 per cent. solution of fluid extract of Veratrum album into jugular vein. *V V* section of vagi one after the other.

FIG. 2.

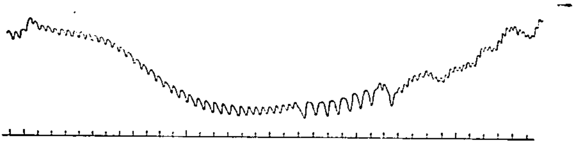


Dog, weight 12.6 kilos. X injection of 1.75 c.c. of 25 per cent. solution of fluid extract of Veratrum viride into jugular vein. *V V* section of vagi one after the other.

As demonstrating this and as showing the similarity of the action of the two drugs, we give two tracings, Figs. 1 and 2. It is certain that the sudden arrest of the heart's action may be due to the influence of the drug upon the heart's muscle; but our results are in accord with those published by Dr. H. C. Wood many years ago, which showed that the main cardiac action of one of the alkaloids is upon the vagi. In this experiment there had been complete paralysis of the pneumogastrics by atropine before the administration of the Veratrum album.

Contrasting the tracing, Fig. 3, with the other records, it will be seen that, although the dose was much larger than was given in Figs. 1 and 2, the fall of pressure was much less and the arrest of the heart's action not complete, so that it would appear as though the drug exerts a double cardiac action, depressing the muscle and at the same time increasing the activity of inhibition.

FIG. 3.



Tracing with mercurial manometer.

Dog, weight 11 kilos. Vagi paralyzed with atropine. × Injection into the jugular of 2 c.c. fluid extract of Veratrum album solution.

As the result of our whole series of experiments, we conclude that the only evidence which we have been able to obtain of differences in the action of Veratrum viride and Veratrum album is that Veratrum album more frequently purges man when taken in toxic doses than does Veratrum viride, and that some specimens of Veratrum album are stronger than are some specimens of Veratrum viride. On the other hand, it would seem, however, probable, or even assured by our experiments that different specimens of Veratrum viride may vary greatly in their strength, and that some specimens of Veratrum viride may be stronger than some specimens of Veratrum album. It is not probable that a clinician would be able to perceive any difference in the action of the therapeutic dose of the two plants, so that it would be proper for the *Pharmacopœia* to recognize both species, if any advantage could be gained by so doing. A national pharmacopœia should, however, according to our thinking, favor the use of American drugs when it can do so without injury to any one. The recognition of Veratrum album would be an aid in the substitution of an American by a foreign drug which now has very little vogue in our markets, and which possesses no advantages whatever over its American representatives. Any difference which may possibly exist between the two Veratrums is in favor of the American drug as less apt to disturb intestinal digestion. Under such circumstances the recognition by the *United States Pharmacopœia* of the European drug seems to us of doubtful expediency.

CRITICAL SUMMARY

OF THE

QUESTION OF FATTY DEGENERATION.

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The question of fatty degeneration, so called, is entangled in the question of the relations of the nitrogenous to the carbonous metabolism as exemplified in the carbohydrates and hydrocarbons. We need to know the following in connection with the processes known as fat metamorphoses: What are these fats? Do they differ from the physiological fats? Whence are they derived? These questions presuppose a knowledge of the physiological fats, their origin, and their uses, and to a certain extent the pathological questions await the solution of the physiological questions. In theory, however, the interdependence need not be complete; even were it shown that physiologically fats are or are not produced from proteids, the contrary would still be possible under pathological conditions. The same holds true for comparative studies; the formation of fat in plants need in no wise correspond to the procedure in animals. Nevertheless, biological reasoning by analogy is of great value, and in the study of fatty degeneration we are largely thrown upon such studies, since direct investigations in connection with diseases are very difficult to institute, and are attended by almost countless opportunities for error and fallacy.

The current pathological teaching is that in fatty degeneration the proteids of the diseased cells become converted into fats. Virchow and Klebs are largely responsible for this, and Klebs's ideas and work were chiefly based upon those of the elder Voit. In general pathological literature no explanation or discussion of worth attends the statement quoted. For this serious error of thus dismissing with an unequivocal statement one of the most fundamental problems of biology there is no excuse, and it constitutes a most flagrant violation of pedagogic principles.